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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/556,440	04/24/00	GJERSET R	INRP:032-2

HM12/1024

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	8

DATE MAILED: 10/24/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/556,440	GJERSET, RUTH A.	
	Examiner	Art Unit	
	Brenda G. Brumback	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 6-26* is/are pending in the application.

4a) Of the above claim(s) *10-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-9 and 18-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is responsive to the amendment filed 08/29/2001. Claims 2-5 were canceled. Claims 1 and 6 were amended.

Election/Restriction

2. Applicant's election without traverse of Group I, claims 1-9 and 18-26, in Paper No. 7 is acknowledged.

3. Claims 1 and 6-26 are pending. Claims 10-17 are withdrawn from consideration as directed to a nonelected invention. Claims 1, 6-9, and 18-26 are under examination.

Information Disclosure Statement

4. The Information Disclosure Statement filed 08/15/2001 (Paper # 4) is acknowledged; however, the cited references were not found in parent file serial number 08/675,887, to the extent indicated on the copy of the PTO-1449 form attached hereto. In order to expedite consideration of the references, applicant may wish to file new copies of those references not considered to date. Any inconvenience is regretted.

Claim Rejections - 35 USC § 112

5. Claims 1, 6-9, and 18-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The article "a" in line 4 of claim 1 renders the claim indefinite, as it is not clear if the recited cell which is contacted with the inhibitory agent is the same cell as the cell into which the expression construct has been introduced or if it is a different cell. It is suggested that "a" be amended to "said" for clarification.

Claim 9 is indefinite as depending from a canceled claim. Correction is required. For purposes of examination, claim 9 has been interpreted as depending from claim 1.

It is suggested that claim 9 be amended to include the full name of the virus denoted by the abbreviation "CMV", *i.e.* cytomegalovirus (CMV), for clarity.

Claim 22 recites the limitation "said subject" in the claim. There is insufficient antecedent basis for this limitation in the claim because the base claim (1) from which claim 22 depends does not recite a subject.

Claim 24 is indefinite as depending from a canceled claim. Claim 26 is also indefinite as ultimately depending from a canceled claim, as it depends from claim 24. For purposes of examination, claim 24 has been interpreted as depending from claim 1. Claim 24 also recites the limitation "said stimulatory agent" in line 1. There is insufficient antecedent basis for this limitation in the claim. Correction is required.

6. Claims 1, 6-9, and 18-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for induction of p53-mediated apoptosis in cells *in vitro*, does not reasonably provide enablement for induction of p53-mediated apoptosis of cells *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of

the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to a method for induction of p53-mediated apoptosis in a cell comprising introducing into the cell an expression construct comprising a nucleic acid encoding p53 with a promotor and contacting the cell with an inhibitory agent that inhibits DNA repair. Dependent claims recite the expression construct as an E1 replication-deficient adenovirus, recite the cell as a tumor cell, and specify that the tumor cell is in a human subject. Thus, the claims encompass gene therapy for cancer by *in vivo* administration of a viral vector.

The state of the prior art and the predictability or lack thereof in the art: Smith (Annu. Rev. Microbiol. 49:807-838, 1995) teaches that there are numerous problems associated with gene therapy, *i.e.*, "definition of the cells that constitute the target, entry of DNA into those cells, expression of useful levels of gene product over an appropriate time period, avoidance of the almost inevitable response of the host to the introduced agents, and so on" (see page 808, last partial paragraph). Smith further teaches specific problems associated with administration of viruses as gene-therapy vectors, such as "the inability of virus to enter into or integrate into chromosomes of particular cells, the shutdown of transcriptional promoters, the loss of input DNA, the destruction of treated cells, and the neutralization of input virus or gene product" (see page 810, first paragraph). Dermer (Biotechnology 12:320, March 1994) teaches that *in vitro* cell culture models are poor predictors of the *in vivo* efficacy of cancer therapeutics because the cell

lines used to model cancer do not mimic conditions in the human body, but rather possess characteristics "profoundly different" from the human disease (see the entire document and especially the second and third paragraphs).

The amount of direction or guidance present and the presence or absence of working examples: Given the teachings found in the art of unpredictability regarding therapeutic administration of viral vectors for gene therapy, and the teachings of unpredictability regarding cell culture models as predictive of *in vivo* efficacy of cancer therapeutics, detailed teachings are required to be present in the instant specification in order to enable one of skill in the art to be able to practice the claimed method for induction of p53-mediated apoptosis in cells *in vivo* for cancer therapy. These teachings are absent. There is no guidance as to how to administer an adenoviral or other viral vector *in vivo* so as to overcome the problems associated with administration of viral vectors for gene therapy. There is no guidance as to how to practice the claimed method so as to achieve p53-mediated apoptosis in a cell within a tumor in a human subject. The working examples are exclusively directed to achieving p53-mediated apoptosis *in vitro* in glioblastoma cells. There are no working examples disclosing *in vivo* administration of a viral vector in conjunction with an agent which inhibits DNA repair for cancer therapy.

The breadth of the claims and the quantity of experimentation needed: Because the claims encompass gene therapy for treatment of cancer *in vivo*, because the art teaches that there is a high level of unpredictability associated with *in vivo* administration of viral vectors and predicting efficacy of a cancer therapeutic *in vivo* based on a cell culture model, and because the

specification does not contain sufficient disclosure to overcome the teachings of unpredictability found in the art, it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 7-9, and 18-20 are rejected under 35 U.S.C. 102(a) as being anticipated by either of Gjerset et al. (Molecular Carcinogenesis 14:275-285, 1995, of record in Paper #4) or Roth et al. (WO 95/28947).

The claimed invention is drawn to a method for induction of p53-mediated apoptosis in a cell comprising introducing into the cell an expression construct comprising a nucleic acid encoding p53 with a promotor and contacting the cell with an inhibitory agent that inhibits DNA repair. Dependent claims recite the expression construct as an E1 replication-deficient adenovirus with a CMV promotor and recite the cell as a brain tumor, glioblastoma, squamous metaplasia, or skin cell (among others).

Gjerset et al. teach a method for sensitizing glioblastoma cells to drug and radiation-induced apoptosis comprising administration of an E1 replication-deficient adenovirus vector comprising nucleic acid encoding wild-type p53 with a CMV promoter in conjunction with either cisplatin or gamma radiation (see the abstract and page 276, third full paragraph).

Roth et al. teach a method for inducing apoptosis in cancerous cells comprising administration of a replication-deficient adenoviral vector comprising a nucleic acid encoding the wild-type p53 tumor suppressor protein with a CMV promotor and a DNA-damaging drug (see the abstract; page 5, line 31, through page 6, line 6; page 7, lines 8-36; page 8, line 20, through page 9, line 3; and page 12, line 4, through page 13, line 10). Roth et al. teach the cancerous cells as tumor cells, squamous metaplasia cells, or other malignant cells (see page 6, line 8, through page 7, line 6).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6-9, 18-21, and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Gjerset et al. (Cancer Gene Therapy, 1/4:330, 1994, Abstract V-87;

hereinafter Gjerset 1994) or Gjerset et al. (Proceedings of the American Association for Cancer Research, 36:36:21, Abstract 123; hereinafter Gjerset 1995) in view of Zhang et al. (Cancer Gene Therapy, 1/1:5-13, March 1994).

The claimed invention is drawn to a method for induction of p53-mediated apoptosis in a cell comprising introducing into the cell an expression construct comprising a nucleic acid encoding p53 with a promotor and contacting the cell with an inhibitory agent that inhibits DNA repair. Dependent claims recite the expression construct as an E1 replication-deficient adenovirus with a CMV promotor; recite the cell as a brain tumor, glioblastoma, or lung cancer cell (among others); and recite delivery of the inhibitory agent by continuous perfusion injection.

Either of Gjerset 1994 or Gjerset 1995 teach a method for induction of p53-mediated apoptosis in a glioblastoma cell comprising introducing into the cell via gene transfer the wild-type *p53* gene and contacting the cell with either cisplatin or gamma radiation. Neither Gjerset 1994 nor Gjerset 1995 specify the method of gene transfer.

Zhang et al. teach that recombinant E1-deficient adenoviral vectors with a CMV promotor are efficient means for gene transfer and high level expression of wild-type p53 tumor suppressor protein in human lung cancer cells (see the abstract and the paragraph bridging pages 9-10).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the adenoviral vector disclosed by Zhang et al. as an efficient means of gene transfer of the wild-type *p53* gene to a cell in the method taught by either of

Gjerset 1994 or Gjerset 1995. Although none of Gjerset 1994, Gjerset 1995, or Zhang et al. disclose administration of the inhibitory agent of DNA repair by continuous perfusion injection, absent some evidence to the contrary, one of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to use continuous perfusion injection as an efficient and effective means of administering the inhibitory agent.

Conclusion

9. No claims are allowed.

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Hamada et al. (Gynecologic Oncology 60:373-379, 1996) teach gene transfer of wild-type *p53* into cervical cancer cells via an E1 replication-deficient adenoviral vector.

Katayose et al. (Clinical Cancer Research 1:889-897, August 1995) teach a recombinant E1 deficient adenovirus vector expressing human wild-type p53 cDNA.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642

and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1642 FAX telephone number is (703)-305-3014. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

BB
October 17, 2001

Brenda Brumback,
Patent Examiner